Review of Literature
In 1801, André del Rio of Mexico City, was the first to recognize a new metal which he named "erythronium" after the red colour of its salts. However, the credit to its discovery goes to Nils Gabriel Sefstrom, who was a Swede. He, along with Berzelius, succeeded in preparing an oxide of this element in 1831 and Berzelius coined this element as "vanadium" (Weeks, 1956). Vanadium and Rick (1927) obtained pure form of this metal, which opened a way to study the physical and chemical properties of this metal. Vanadium(V) is a bright white ductile metal with melting point of 1,980 ± 10°C, boiling point of 3,380°C at 1 atm, and specific gravity of 6.14 at 18.7°C temperature (Weast, 1970).

CHEMISTRY OF VANADIUM

Vanadium is a transition element and belongs to group Va, hence having five valence electrons and giving rise to a maximum oxidation state of +5. A number of
Vanadium compounds are known, in which vanadium exists in the oxidation states of 0, +2, +3, +4 and +5. It is most stable in the +4 and +5 valence states. Discrete $V^{4+}$ and $V^{5+}$ ions are not known to exist and vanadium is usually found bound to oxygen as a negatively charged polymeric oxyanion that tends to complex to polarizable ligands such as phosphorus and sulfur (Buckingham, 1973; Clark, 1973). Vanadium in the +5 oxidation state is reduced to vanadium +4 by relatively mild reducing agents. It is the most stable oxidation state of vanadium. Johnson et al (1974) reported that rats injected with vanadium in the +5 oxidation state contained vanadium in the +4 oxidation state in their tissues. Vanadium in the +3 oxidation state, as $V_2O_3$ is completely basic and dissolves in acid to give the green hexaaquo ion $[\text{V(H}_2\text{O)}_6]^3+$. This species probably accounts for the "green tongue" that is symptomatic of acute exposure to vanadium. Several bright green complexes of vanadium +4 are also known (Cotton and Wilkinson 1962, Durrant and Durrant 1970) which might account for the green tongue symptom.

DISTRIBUTION:

Vanadium is one of the most abundant trace elements in nature. Its geochemical and biochemical behaviour is primarily a function of oxidation state (Goren 1966). The main source of vanadium in soil is parent rocks from which the soils are formed. Vanadium levels were reported from
3 to 310 μg/g in different soil samples, the highest being in shales and clay (Vinogradov 1959, Cannon 1963, Pratt 1966). In fresh water, the concentration of vanadium is largely dependent upon the extent of leaching from soil and rocks, and here it is oxidised from the trivalent to the most soluble pentavalent state during leaching process. An average vanadium concentration of 40 μg/l with a range of 2-300 μg/l was reported in samples of fresh water (river, lakes) and below 10 μg/l in drinking water (Durfor and Becker 1963, Kopp and Kroner 1968).

The use of fossil fuel in various industrial operations such as iron and steel industries, thermal power plants and metallurgical processes, leads to an increase in the concentration of vanadium in their close physical environment (Parker et al. 1978, Patel and Pandey 1985). Besides this, the wide spread usage of vanadium in many fields such as manufacture of pigments and insecticides also leads to an increase in vanadium concentrations in the environment (Hudson 1964, Hammond and Beliles 1980).

Vanadium is widely distributed in plant and animal kingdom (Vinogradov 1959, Schroeder 1970a). In many cases the vanadium content of plants, animals and humans is directly related to the physical environment in which they are present (Bertrand 1950, Schroeder 1970a). The highest concentration of vanadium is found in certain marine organisms such as sea squirts (e.g. Phallusia mammula - 1,900 μg/g), sea cucumber (Sticopus moesii - 1,200 μg/g).
and a mollusk (*Pleurobranchus Plumula* - 150 μg/g). In certain ascidians, the trivalent vanadium is present as chromoprotein called hemovanadin with sulphuric acid in green cells called vanadocytes, whereas in other ascidians, it is present free in plasma (Hudson 1964).

**Essentiality of Vanadium:**

Vanadium is found to be essential for the mold *Aspergillus niger* (Bertrand 1942) and is thought to play a role in photosynthesis in the green algae *Scenedesmus obliquus* (Arnon and Wessel 1953, Arnon 1958). At high temperatures the yeast *Candida slooffii* requires vanadium (Roitman et al 1969). Vanadium uptake by yeast cells was reported by Bode et al (1990). The growth of *Mycobacterium tuberculosis* was found to diminish in presence of the vanadium as V₂O₅ (Kopylova. 1967). Vanadium in soil is said to interfere with nitrogen fixation (Horner et al 1942, Takahashi and Nason 1957, Nason 1958,彼得burgski et al 1975).

Trace amounts of vanadium are apparently essential for chick and rat. Vanadium deficiency in chick and rat was demonstrated by several investigators (Hopkins and Mohr 1971, Schwarz and Milne 1971, Štrasis 1971, Nielsen and Cilrion 1973) which leads to significant reduction in feather growth in chickens and impaired fertility with marked reduction in offspring in third and fourth generations (Hopkin and Mohr 1974). A dietary requirement of
100 μg/kg of vanadium was essential to maintain normal growth in rats (Hopkins and Mohr 1974).

**HUMAN INDUSTRIAL EXPOSURE:**

Dutton (1911) was the first to describe the health effects of industrial exposure to vanadium-bearing ores. He reported a dry paroxysmal cough with hemoptysis and anemia. A generalised systemic action of vanadium showing severe conjunctivitis, rhinitis, chronic productive cough, wheezing, tightness of chest, tremors of fingers, palpitation, and green tongue was reported in industrial workers exposed to vanadium dust (Symanski 1939, Rundberg 1939, Balestra and Molfino 1942, Wyers 1946, 1948, Kiviluoto 1980). A detailed report was presented on dust content of air in metallurgical plants producing vanadium pentoxide with similar clinical findings (Sjoberg 1955, Sjoberg and Ringer 1956). Clinical symptoms such as sneezing, nasal discharge and sore throat followed by secondary symptoms like dry cough, wheezing, difficulty in breathing, lassitude, anemia and depression have been reported in workers involved in boiler cleaning (Frost 1951, Williams 1952, Nickling 1958, Roshchin 1962, 1966, Troppens 1969, Kiviluoto 1980). Troppens (1969) described the first symptom as swelling of face and eyes as early as 20 minutes after entering the boiler area which disappeared after removal from exposure area for 2-3 weeks. The vanadium concentration of serum and urine of the workers exposed to vanadium has been shown to have a direct relation with air-borne
vanadium levels to which they are exposed (Kiviluoto 1981, White et al 1987, Kawai et al 1989). It has been reported that vanadium exposed workers are more susceptible to cold and other respiratory illness (Roshchin 1962, 1967, Schumann Vogt 1969, Troppens 1969, Cohen Mitchell D. et al 1989). Recent studies by Waters et al (1974, 1975) have demonstrated that vanadium salts are toxic for alveolar macrophages in vitro. In view of the role of alveolar macrophage in pulmonary defence, vanadium exposure may impair resistance of lungs to infection.

**TOXICOLOGICAL EFFECTS OF VANADIUM IN EXPERIMENTAL ANIMALS:**

Priestley (1876) showed that sodium vanadate solution given to pigeon, guinea pig, rat and rabbit by different routes has the effect on central nervous system causing drowsiness with convulsion followed by gradual paralysis of respiration and motion, which was further substantiated by others (Larmuth 1877, Bowdeshwell 1878). Proescher et al (1917) reported the lethal effect of different vanadium preparations affecting the central nervous system as well as renal system; and pulmonary haemorrhage in mice, rat, guinea pigs and rabbits. The toxicity of vanadium depends on its valency, and it increases with the increase of valency. The toxicity also depends on the mode of administration, i.e., low by oral route, moderate by the respiratory route and high by intravenous route. The smaller animals, i.e., rat and mouse, tolerate the metal fairly well, but rabbit, horse and man, are more sensitive to vanadium.
The toxicity of vanadium salts to organisms was recorded by several investigators in experimental animals, i.e., rat, mouse, rabbit, and also in man (Massmann 1956, Browning 1962, Schroeder et al 1963, Hudson 1964, Schroeder 1970, Sone, Ken 1981, Cheng-y et al 1982, Llobet and Domingo 1984). An oral administration of ammonium vanadyl tartrate to human beings did not have much effect, except cramps and diarrhoea (Diamond et al 1963). The vanadium toxicity has been reported in different fishes by several workers (Proescher 1917, Tarzwell and Henderson 1960, Knudston 1979 and Dhurandhar 1988). NaV\textsubscript{3}O\textsubscript{7} was reported to be neither embryolethal nor teratogenic in rats, when administered orally at 20 mg/kg/day to pregnant rats from 6th to 14th day of pregnancy (Paternain et al 1987). However, Mariann (1984) reported that vanadium interfered with fetal skeletal ossification and fetal development in the mouse. Dietary vanadium reduced egg production, egg weight, body weight, feed consumption and shell quality in egg laying hens (Gusterhout and Berg 1981, Kubena and Phillips 1983, Cupo Michael and Donaldson 1987). Vanadium effect was studied on endocrine organs in pigeon (Columba viva intermedia) and it was found that vanadium treatment causes vacuolation with increased granulation in cyanophils and depletion of granules in the lead-haematoxylin positive cells of the pituitary gland and increased activity of thyroid follicles. The testicular tubules and interstitial cells were hypertrophical, whereas the ovaries showed follicular atresia (Divan and Belsare 1987).
The toxicological study of vanadium in rabbits was investigated by various workers which mainly deals with respiratory exposure to vanadium pentoxide (Sjoberg 1950, Gulko 1956, Hoshchin 1963, Pazynich 1966). Sjoberg (1950) reported in great details of the experiments in which rabbits were exposed to vanadium pentoxide dust. High concentrations over short periods of time were relatively toxic, i.e., 205 mg V$_2$O$_5$/m$^3$ (or 115 mg/V m$^3$) was found to be lethal in 7 hours. At these levels, tracheitis was marked, and it was accompanied by pulmonary edema and bronchopneumonia, conjunctivitis, enteritis and fatty infiltration of the liver. Vanadium was detected in ashed lung, liver, kidney and intestine. Gulko (1956) found that continuous exposure of rabbits to 10–30 mg V$_2$O$_5$/m$^3$ (5.6 to 16.8 mg V/m$^3$) was toxic and caused bronchitic pneumonia, loss of body weight and bloody diarrhea. Acute inhalation of vanadium by rats was characterized by irritation of the respiratory mucosa, nasal discharge, difficulty in breathing, weight loss as well as dysentry, paralysis of the hind limbs, respiratory failure and death in case of severe poisoning (Hoshchin 1963, 1967).

Metabolic Alterations:

Marked changes in fat content were reported in the liver of dogs and cats poisoned by ammonium metavain date (Dowdeswell 1874). Lyonnet et al (1899) recorded an increased urea excretion in patients treated with sodium vanadate, believing that some cellular oxidations were
promoted by this salt. An increased levels of nitrogen, sulphur and phosphorus were observed in the urine of men who were administered 50 mg of vanadium pentoxide intramuscularly indicating that the vanadium stimulated the metabolism (Proescher et al 1917). A decreased level of cystine content of rat hair, fed with 25 to 1,000 ppm of vanadium was recorded. Similarly a decreased level of cystine content in the finger nails of vanadium exposed workers was also noted (Mountain et al 1953, 1955). A decreased concentration of CoA and thioctic acid was found in the liver of the rats receiving sodium metavanadate by diet and intraperitoneal injection (Mascitelli-Coriandoli and Citterio 1959a and 1959b). Curran (1954) was the first to report that vanadium depressed the incorporation of isotope-labelled acetate into liver cholesterol in vivo and in vitro. Subsequently, it was observed that the site of inhibitory action of vanadium was at the level of squalene synthetase (Azarnoff and Curran, 1957, Azarnoff et al 1961). Vanadium was also shown to mobilize aortic cholesterol in atherosclerotic rabbits more rapidly as compared to control (Curran and Costello, 1956). Curran et al (1959) conducted a clinical study, in which five normal adult males were fed 150-200 mg/day soluble diammonium oxy-tartratovanadate (20-30 mg V/day) for 6 weeks, and recorded significantly reduced plasma cholesterol. However, Lewis (1959a) studied vanadium exposed workers and reported slightly lower serum cholesterol than controls. Patients given vanadium salt did not show statistically significant lowered level of
cholesterol (Somerville and Davies, 1962, Diamond et al 1963, Schroeder et al 1963). Curran and Burch (1967) suggested that a regulatory enzyme of cholesterol biosynthesis, acetoacetyl coenzyme A deacylase is activated in young animals and inhibited in older ones by vanadium. After exposing the group of rabbits to a grinding aerosol of vanadium trioxide (45-75 mg/m$^3$, 2 hr/day, 12 months), there was a progressive weight loss, decline in leucocyte count, serum ascorbate and haemoglobin, monoamine oxidase activity and increased blood cholinesterase activity (Roshchin 1963, 1967, Roshchin et al 1965, Johnson et al 1974). Roshchin (1967) also pointed out that vanadium is an inhibitor of the monoamine oxidase activity (which converts serotonin to 5-hydroxyindoleacetic acid) and suggested that inhibition of monoamine oxidase may result in accumulation of serotonin in the central nervous system, leading to functional disturbances. Pazynich (1966) exposed the rats for 70 days through continuous inhalation and reported depressed whole blood cholinesterase and serum $\beta$-globulin.

Aiyar and Sreenivasan (1961) reported that vanadium salts inhibit succinate dehydrogenase which would reduce $ATP$ synthesis. Wright et al (1960) observed that vanadium uncouples mitochondrial oxidative phosphorylation in liver homogenates in vitro, resulting in depletion of ATP energy stores. Vanadium metaventalate given in the diet (25 $\mu$g/g vanadium) was reported to uncouple oxidative phosphorylation in liver mitochondria of young chicks (Hitchcock et al

Vanadium intoxication causes changes in brain catecholamine levels in rats (Witkoska Brzezinski 1979). Changes in the blood levels of urea, uric acid and total protein was observed in rats, in a dose dependent manner, which were given vanadium in their drinking water for 3 months (Longo et al 1985). Ramsarma et al (1981) reported that rate of NADH oxidation with oxygen is stimulated 10 to 20 fold in presence of vanadium. Further, Liochev and Todorovic (1990) observed that vanadate stimulated the oxidation of NAD(P)H in the presence of
biological membranes and other sources of oxygen. Dickson and Stern (1990) reported that tetravalent vanadium mediated the oxidation of low density lipoprotein. Vanadium induced changes were reported in glycogen content in fishes (Jagadeesh et al 1989). Recent studies indicate that vanadate stimulates the 2,3-diphosphoglycerate phosphatase of human erythrocytes as well as oxygen consumption and tyrosine phosphorylation in electropermeabilized human neutrophils (Sergio Grinstein et al 1990, George et al 1990).

It has been observed that vanadate produced an insulin-like stimulation of adipocyte glucose oxidation (Tolman et al 1979, Dubyak & Kleinzeller 1980, Tamura et al 1984). However, Bosch et al (1987) reported that vanadate inactivated rat hepatocyte glycogen synthetase and activated glycogen phosphorylase in a dose and time-dependent manner. Thus in the hepatocyte, vanadate exerts opposite effects than in the adipocyte and skeletal muscle, where it has an insulin like effect. It has been further reported that vanadate normalizes blood glucose level in experimental diabetes (Meyerovitch et al 1987, Kantnaswamy et al 1988). Several workers have reported the insulin-mimetic effects of vanadium and its possible implication for further treatment in diabetes (Ramanadham et al 1990, Sekar et al 1990, Daphne, Schechter 1990). Lieffetz et al (1990) reported that the insulinomimetic agents N\textsubscript{2}O\textsubscript{2} and vanadate stimulate protein tyrosin phosphorylation in intact cells.